Ethical issues in international collaborative research

Reidar K. Lie, M.D., Ph.D.

Department of Clinical Bioethics, NIH, USA

Disclaimer

- The opinions expressed are the author's own. They do not reflect any position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services

Special concerns

- Different regulations
  - Children
  - Emergency Research
  - Informed consent requirements
- Different scientific judgments
  - Hypoxis trial
- Different cultural traditions
  - Individual informed consent

Ethics & resources

- Ethical issues that arise when conducting research in resource poor settings, relative to economic conditions of sponsor country
- Specifically, ethical issues that arise because trial participants will receive less care during and after trial than trial participants would in sponsor country

Common position

- One has an obligation to provide same standard of care in trial as is provided in resource rich settings
- One has an obligation to treat other conditions that arise during the trial
- One has an obligation to continue to provide study medication to trial participants if found to be effective
- One has an obligation to continue to treat conditions identified as part of research, even after trial is completed

Need for specifics

- We all agree that it is important to do as much as we can to improve medical care to participants in trials
- We also agree that we should try to do as much as we can to improve care in general in resource poor settings
- But, because we typically have competing concerns, we typically are not able to do everything we want to do, and we need to weigh the competing concerns appropriately to decide what to do specifically in the context of research carried out in resource poor settings

Examples of competing concerns

- Conflict between wanting to provide a standard of care available in resource rich settings and wanting to do a trial that will yield useful results in a resource poor setting
- Conflict between spending scarce resources on treating patients with immediate needs now versus using those funds to do research that will yield results that can help future patients

Three distinctions

- Moral concerns at different time periods during the course of a research project
- Different level of moral requirements
- Different types of provision of care to study participants and others

Time periods

- **What should one require before study starts, as a *condition* for *approving* the study**
- What is one obligated to do when events occur during the study
- What is one obligated to do once the results of the study are known

Degrees of moral requirements

- **Interventions that should be obligatory**
  - Participants denied life saving treatment in control group that they would receive outside the trial
- Interventions that are morally praiseworthy

Three types of cases of provision of care

- Standard of care
  - Necessary care for scientific design of trial
  - Trial intervention, control intervention
- Ancillary care obligations
  - Additional care provided to trial participants
- Post-trial benefits to trial participants
  - Intervention identified as effective in the trial
  - Other interventions (HIV treatment for those who seroconvert in non-HIV treatment trials)

Standard of care issues

- Presumption: provide best current treatment to control group
  - Independent of place of trials
- Many will allow exceptions: two conditions:
  - Scientifically necessary
  - In order to obtain results useful for country where trial takes place

Standard of care: Examples

- Trials to test interventions to prevent HIV transmission during breastfeeding
  - Formula feeding known to prevent transmission
- Development of useful diagnostic tests to monitor HIV treatment in resource poor settings
  - Viral load known to be reliable monitoring tool

Ancillary care: examples

- Diagnosis and treatment of malaria in a basic science study of malaria pathogenesis
- Diagnosis and treatment of HIV related illnesses in a basic science study of malaria pathogenesis
- Treatment of HIV infection in trials of perinatal HIV transmission

Justification?

- On what basis do we justify a plan to provide care for specific conditions, before trial starts?
- This justification may be different from that involving a researcher deliberating about what to do when confronted with a study participant who needs care
- And should provide a justification strong enough to reject the study if a credible plan for the care is not provided before the study starts

Post-trial obligations: participants

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by that study
  - Helsinki-2000

Pre-approval condition

- What should we require, as a condition of IRB approval, before the trial starts:
  - Guaranteed access to study medication after study is completed?
    - A legally binding agreement?
    - Money in the bank to buy study medications?
    - Letter of intent by Ministry of Health?
    - Memorandum of understanding of treatment clinic?
    - Explore various options before trial starts

South African case

- Pharmaceutical company wants to do a treatment trial of a new promising drug combination
- Ethics committee requires that those who benefit receive the drug combination as long as they benefit afterwards
- Company says no: it is too costly, partly because they have to buy rival company drugs
- Activist community wants the trial

NIH ARV Guidance

- For antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment
- Applicants are expected to provide NIH Program Staff for evaluating their plans that identify available sources, if any, for provision of antiretroviral treatment to research participants
- Priority may be given to sites where sources are identified for provision of ARV treatment

Post-trial obligations in preventive trials

- Treatment of HIV in HIV preventive trials
  - Sero-converters in HIV vaccine trials
- Treatment of HIV in non-HIV trials
  - Participants who are screened for HIV during TB trials

Justification

- If we think that it is not obvious that one should require a guarantee before study starts
- If one thinks that it is not obvious that HIV treatment should take automatic precedence to other health needs
- Then one needs a justification for what is required that would enable us to weigh the various concerns appropriately

Post-trial obligations to wider community

Blood pressure trial in India

- Pharmaceutical company wants to do a trial of a new blood pressure drug in India. A new version of an existing drug whose safety profile is well established
- They want to do it India because it is $200 m cheaper to do it there
- Drug will be sold almost exclusively in Western Europe and North America

Malarone trial in Indonesia

- Trial to establish the effect of malarone on prevention of malaria
- Proposed for a malaria endemic region of Indonesia.
- Placebo controlled trial. Observe number of malaria cases in the two groups
- Number of safety measures in place
- Community wants it because of health benefits

Two positions

- We only need to be concerned about safety, risks and benefits to the participants in trial. If that is favorable, the trial should be approved
- Only approve research if there is a chance that the trial results will be useful for the host country or that there is a guarantee of reasonable availability

Helsinki

- Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research

CIOMS

- As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to the inhabitants of the underdeveloped community in which the research was carried out. Exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun

Fair benefits framework

- All benefits and risks need to be evaluated
  - Benefits and risks to research participants
  - Benefits to general community during trial
  - Benefits after the completion of the trial
- Community involvement
  - Involvement at all level of decision making
  - Uncoerced
- Transparency in decision making